PATENT
Attorney Docket No **UM-06106**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Lubman *et al.*
Serial No.: 09/778,496 Group No.: 1631
Filed: 02/07/2001 Examiner: Mahatan
Entitled: **Mapping Of Differential Display Of Proteins**

TRANSMITTAL OF APPEAL BRIEF (PATENT APPLICATION - 37 CFR § 192)

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)
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Dated: June 20, 2005 **By:** Mary Ellen Waite

Sir or Madam:

1. Transmitted herewith, in triplicate, is the APPEAL BRIEF in this application, with respect to the Notice of Appeal filed concurrently with this application.

2. STATUS OF APPLICANT

This application is behalf of other than a small entity.

3. FEE FOR FILING APPEAL BRIEF

Pursuant to 37 CFR § 1.17(g), the fee for filing the Appeal Brief is: $500.00

4. EXTENSION OF TERM

The proceedings herein are for a patent application and the provisions of 37 CFR § 1.136 apply.
Applicant petitions for a one month extension of time under 37 CFR § 1.136 (fees: 37 CFR §§ 1.17(a)-(d)).

Fee for Extension of Time $120.00

4. TOTAL FEE DUE

The total fee due is:

Appeal brief fee $500.00
Request for One Month Extension of Time $120.00

TOTAL FEE DUE $620.00

5. FEE PAYMENT

Attached is a check for $620.00.

6. FEE DEFICIENCY

If any additional fee is required, charge Account No. 08-1290.

Dated: June 20, 2005

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06-21-05

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PATENT

Attorney Docket No.: **UM-06106**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Lubman, *et al.*		
Serial No.:	09/778,496	Group No.:	1631
Filed:	02/07/01	Examiner:	Mahatan
Entitled:	**MAPPING OF DIFFERENTIAL DISPLAY OF PROTEINS**		

APPELLANTS' BRIEF

APPEAL NO.:

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Commissioner for Patents and Trademarks
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P.O. Box 1450
Alexandria, VA 22313-1450

Dated: June 20, 2005

By: _____
Mary Ellen Waite

Sir:

This Brief is in furtherance of the Notice of Appeal filed March 16, 2005.

The fees required under § 1.17(h) and any required Petition for Extension of Time for filing this Brief and fees therefore are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This Brief is transmitted in triplicate. [37 C.F.R. § 1.192(a)].

This Brief contains these items under the following headings and in the order set forth below [37 C.F.R. § 1.192(c)]:

I. REAL PARTY IN INTEREST

The real party in interest is The Regents of the University of Michigan.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to Appellants, Appellants' legal representative, or the Assignee.

III. STATUS OF THE CLAIMS

Claims 1 - 34 were filed in the original application. During prosecution of the application, Claims 7 and 25 were canceled and new Claims 35-37 were added. Claims 1-6, 8-24, and 26-37 have been rejected by the Office in the Final Office Action dated November 17, 2005. Therefore, Claims 1-6, 8-24, and 26-37 are currently pending and are herein appealed. No other claims are pending. Thus, Appellants appeal the Final Office Action of November 17, 2004. The Claims, as they now stand, are set forth in Appendix A.

IV. STATUS OF THE AMENDMENTS

There are no pending amendments not entered into the record.

V. SUMMARY OF THE INVENTION

The present invention relates to protein separation systems and methods useful for resolving and characterizing large numbers of cellular proteins. In particular, the present invention provides novel mass mapping systems and methods for the differential display of proteins.

In particular, the present invention provides a method of producing protein profile maps. The method includes the steps of providing a first sample comprising a plurality of proteins; a second sample comprising a plurality of proteins; a separating apparatus, wherein the separating apparatus separates proteins based on a physical property; a mass spectroscopy apparatus. The method also includes the step of treating the first and second samples with the separating apparatus to produce a first separated protein sample and a second separated protein sample, wherein the first and second separated protein samples are collected from the separating

apparatus in a plurality of fractions, each of the fractions defined by a physical property; and analyzing the plurality of fractions from each of the first and second separated protein samples with the mass spectroscopy apparatus to produce a protein profile map for each of the first and second samples. The protein profile maps display protein abundance and mass of the first protein sample and the second protein sample where each protein is displayed as a separate band corresponding to the mass of the first protein sample and the second protein sample the intensity of the band corresponds to the protein abundance of the first protein sample and the second protein sample. The protein profile maps for each of the first and second samples are displayed side by side. The method is described, for example in Examples 2 (page 31, line to page 34, line 26) and 3 (page 35, line 1- page 40, line 12) and the Specification, at pages 19, line 1- page 20, line 26. In some embodiments, the an automated sample handling that transfers the first and second samples to the separating apparatus and from the separating apparatus to the mass spectrometry apparatus is linked to the separating apparatus and the mass spectroscopy apparatus (described, for example, in the Specification at pages 21, lines 11-28). In some embodiments, the automated sample handling device, the separating apparatus, and the mass spectroscopy apparatus are linked to a centralized control network that controls their operations (described, for example, in the specification at Pages 21, lines 11-28). A centralized control network having computer memory and a computer processor is described, for example, in the specification at Pages 21, lines 11-28.

A first sample comprising a cell lysate from a first cell type and a second sample comprising a cell lysate from a second cell type is described, for example, in Example 3 (page 35, line 1 - page 40, line 12) and in the Specification at Page 24, lines 3-28. Embodiments where the first cell type is a cancerous cell type and the second cell type is a non-cancerous cell type are described, for example, in Example 3 and in the Specification at Page 24, lines 3-28. Bands of different colors are described, for example, in the Specification on page 20, lines 1-16. Methods where protein abundance and mass are indicative of the cell type of said protein sample in Examples 2 (page 31, line 8 - page 34, line 26) and 3 (page 35, line 1 - page 40, line 12). Determining the identity of individual bands on a protein profile map is described, for example in Example 2 (page 31, line 8 - page 34, line 26). The step of treating the first sample with an external agent prior to treating the first and second samples with the separating apparatus is

described, for example, in Example 2 (page 31, line 8 - page 34, line 26). The external agent comprising estradiol is described, for example, in Example 2 (page 31, line 8 - page 34, line 26).

An automated sample handling device comprising a switchable, multi-channel valve is described, for example, in the specification at Page 14, lines 3-12. A method where the first and second samples further comprise a buffer for solubilization of the first and second protein samples and wherein the buffer is compatible with the separating apparatus and the mass spectroscopy apparatus is described, for example, in the specification on page 13, lines 12-23. A buffer comprising a compound of the formula n-octyl C_6-C_{12} glycopyranoside (e.g. n-octyl ß-D-glucopyranoside or n-octyl ß-D-galactopyranoside) is described, for example, in the specification at page 17, lines 7-16.

The separating apparatus being a liquid phase separating apparatus is described, for example, in Example 2 (page 31, line 8 - page 34, line 26) and 3 (page 35, line 1 - page 40, line 12) in the specification, at page 10, lines 8-28, page 12, lines 7-16, and pages 16-17. The liquid phase separating apparatus comprising a reverse phase HPLC separating apparatus is described, for example in Example 2 (page 31, line 8 - page 34, line 26) and in the Specification at page 10, lines 16-28 and pages 16-17. The reverse phase HPLC comprising non-porous reverse phase HPLC is described for example, in Example 2 (page 31, line 8 - page 34, line 26) and in the specification at page 10, lines 16-28 and pages 16-17. In some embodiments, prior to analyzing the first and second separated protein samples by mass spectroscopy, the first and second samples are divided into first and second portions and wherein and second portions are subjected to enzymatic digestion (described, for example, in the specification on page 18, line 28-page 19, line 11). Analyzing the first and second separated protein samples by electrospray ionization-orthogonal acceleration-time-of-flight mass spectrometry is described for example, in Example 2 (page 31, line 8 - page 34, line 26) and the specification on page 18, line 11 - page 19, line 15. Analyzing the first and second separated protein samples by a mass spectrometry technique of ion trap mass spectrometry, ion trap/time-of-flight mass spectrometry, quadrupole and triple quadrupole mass spectrometry, Fourier Transform (ICR) mass spectrometry, or magnetic sector mass spectrometry is described, for example, in the specification on page 18, lines 21-27.

The present invention further provides a method of comparing protein profile maps. In some embodiments, the method includes the steps of providing a cell lysate comprising a

plurality of proteins derived from a cell of unknown type, a first protein profile map generated by the method described above; a separating apparatus that separates proteins based on a physical property; and a mass spectroscopy apparatus. The method further comprises the step of treating the cell lysate with the separating apparatus to produce a separated protein sample; wherein the separated protein sample is collected from the separating apparatus in a plurality of fractions, each of the fractions defined by a physical property; analyzing the plurality of fractions from the separated protein sample with the mass spectroscopy apparatus to produce a second protein profile map, wherein the second protein profile maps displays each protein as a separate band corresponding to the mass of said first protein sample and the second protein sample, and wherein the intensity of the band corresponds to said protein abundance of the first protein sample and the second protein sample; and comparing the first protein profile map and the second protein profile map, wherein the first and second protein profile maps are displayed side by side. The method is described, for example, in Examples 2 (page 31, line 8 - page 34, line 26) and 3 (page 35, line 1 - page 40, lone 12). A first protein profile map displaying protein abundance and mass from cell lysates of several known cell types and a second protein profile map displaying protein abundance and mass from a cell lysate of an unknown type is described, for example, in the specification on page 10, lines 3-6 and Example 3 (page 35, line 1 to page 40, line 12). Bands of different colors are described, for example, in the Specification on page 20 lines 2-5. Methods where protein abundance and mass are indicative of the cell type of said protein sample in Examples 2 (page 31, line 8 - page 34, line 26) and 3 (page 35, line 1 - page 40, line 12).

A system for the production of a data representation of a protein profile map, comprising a non-porous reverse phase HPLC separating apparatus; an automated sample handling apparatus configured to receive first and second separated protein samples from the reverse phase HPLC separating apparatus; a mass spectroscopy apparatus configured to receive proteins from the automated sample handling apparatus; and a processor configured to produce a data representation of a protein profile map for the first and second separated protein samples analyzed by the mass spectroscopy apparatus. The protein profile map displays protein abundance and mass of a separated protein sample, wherein the protein profile map displays proteins as separate bands corresponding to the protein abundance and mass of the separated

protein sample, and wherein the intensity of the bands corresponds to the abundance of the proteins, wherein the protein profile maps for each of the first and second samples are displayed side by side. They system further comprises a display apparatus that displays the protein profile maps. The system is described, for example, in the specification on pages 15-23. A protein profile map displaying protein abundance as bands of varying intensity is described, for example, on page 20, lines 2-16. Bands of different colors are described, for example, in the Specification on page 20, lines 2-5. Methods where protein abundance and mass are indicative of the cell type of said protein sample in Examples 2 (page 31, line 8 - page 34, line 26) and 3 (page 35, line 1 - page 40, line 12). A processor configured to determine the identity of individual bands on the protein profile map is described, for example in the specification on page 21, lines 20-28. An automated sample handling device comprising a switchable, multi-channel valve is described, for example in the specification on page 13, line 24 to page 14, line 21. A mass spectrometry apparatus comprising an electrospray ionization-orthogonal acceleration-time-of-flight mass spectrometry apparatus is described for example, in Example 2 (page 31, line 8 - page 34, line 26) and the specification on page 18, line 11 - page 19, line 15.

In certain embodiments, the present invention describes a method of producing protein profile maps. The method comprises providing a first sample comprising a plurality of proteins; a second sample comprising a plurality of proteins; a separating apparatus, wherein the separating apparatus separates proteins based on a physical property; and a mass spectroscopy apparatus. The method further comprises the steps of treating the first and second samples with the separating apparatus to produce a first separated protein sample and a second separated protein sample, where the first and second separated protein samples are collected from the separating apparatus in a plurality of fractions, each of the fractions defined by a physical property; analyzing the plurality of fractions from each of the first and second separated protein samples with the mass spectroscopy apparatus to produce first and second protein profile maps for each of the first and second protein samples, where the protein profile maps display protein abundance and mass of the first protein sample and the second protein sample; and displaying a differential display protein map of the first and second protein profile maps, where the differential display protein map displays the difference in protein abundance versus mass between proteins in the first and second protein samples, and where the differential display

protein profile map displays the difference in protein abundance between each protein as a separate band corresponding to the mass of the first protein sample and the second protein sample, and where the intensity of the band corresponds to the difference in protein abundance. The method is described, for example, in Examples 2 (page 31, line 8 - page 34, line 26) and 3 (page 35, line 1 - page 40, line 12) and in the specification on pages 15-23. Displaying the first and second protein profile maps is described, for example, in Example 3 (page 35, line 1 - page 40, line 12) and in the specification on page 19, line 17 to page 21, line 10. Side by side display of the first and second protein profile maps and the differential display map is described, for example, in Example 3 (page 35, line 1 - page 40, line 12) and Figure 5.

VI. ISSUES

There are three issues involved in the present appeal:

Issue 1 – Whether Claims 1-6, 8-20, 22-24, and 26-33 are obvious over Chong et al. (Rapid Commun. Mass Spectrometr. 12:1986 [1998]); hereinafter Chong) in view of Richmond et al (Richmond et al., J. Chromatography 835:29 [1999]; hereinafter Richmond);

Issue 2 – Whether Claims 35-37 are obvious light of Chong taken in view of Richmond and further in view of Pandey et al. (Nature 405: 837 (2000); hereinafter Pandey); and

Issue 3 - Whether Claims 1-6, 8-24 and 26-34 are obvious in light of Chong taken in view of Richmond and further in view of Verentchikov (U.S. Patent 6,534,764; hereinafter Verentchikov).

VII. GROUPING OF CLAIMS

Certain Claims stand alone, with separate limitations and must be considered independently. Other Claims stand and fall together in view of the present cited references. The grouping of each claim is presented below.

Claims 1, 5, 6, 8, 9, 10, 14, 17, 18, 19, 20, 21 22, 23, 24, 26, and 27 stand or fall together. Independent Claim 1 specifies a method of producing protein profile maps, comprising: providing a first sample comprising a plurality of proteins; a second sample comprising a plurality of proteins; a separating apparatus, wherein said separating apparatus separates proteins based on a physical property; a mass spectroscopy apparatus; and treating said first and second

samples with said separating apparatus to produce a first separated protein sample and a second separated protein sample, wherein said first and second separated protein samples are collected from said separating apparatus in a plurality of fractions, each of said fractions defined by a physical property; and analyzing said plurality of fractions from each of said first and second separated protein samples with said mass spectroscopy apparatus to produce a protein profile map for each of said first and second samples, wherein said protein profile maps display protein abundance and mass of said first protein sample and said second protein sample, and wherein said protein profile maps displays each protein as a separate band corresponding to said mass of said first protein sample and said second protein sample, and wherein the intensity of said band corresponds to said protein abundance of said first protein sample and said second protein sample; and wherein said protein profile maps for each of said first and second samples are displayed side by side.

Dependent Claim 2 specifies the method of Claim 1, further comprising an automated sample handling device operably linked to said separating apparatus and said mass spectroscopy apparatus, wherein said sample handling device transfers said first and second samples to said separating apparatus, and wherein said sample handling device transfers said first and second separated protein samples from said separating apparatus to said mass spectroscopy apparatus. Thus, prior art must further teach an automated sample handling device. The cited art, to the extent that it teaches or suggests all of the elements of Claim 1 (Appellant contends that it does not), does not teach a sample handling device as claimed in Claim 2. Thus, Claim 2 would be patentable where Claim 1 was not (Appellant contends that Claim 1 is patentable).

Dependent claims 3 and 4 stand and fall together and specify (claim 3) the method of Claim 2, further comprising a centralized control network operably linked to said automated sample handling device, said separating apparatus, and said mass spectroscopy apparatus, wherein said centralized control network controls the operations of said automated sample handling device, said separating apparatus, and said mass spectroscopy apparatus and (Claim 4) the method of Claim 3, wherein said centralized control network comprises computer memory and a computer processor. The cited art, to the extent that it teaches or suggests all of the elements of Claim 2 (Appellant contends that it does not), does not teach a centralized control network optionally comprising computer memory and a computer processor as claimed in Claims

3 and 4. Thus, Claims 3 and/or 4 would be patentable where Claim 2 was not (Appellant contends that Claim 2 is patentable).

Dependent Claim 11 specifies the method of Claim 6, further comprising the step of treating said first sample with an external agent prior to treating said first and second samples with said separating apparatus. The cited art, to the extent that it teaches or suggests all of the elements of Claim 6 (Appellant contends that it does not), does not teach a method that comprises the step of treating the first sample with an external agent as claimed in Claim 11. Thus, Claim 11 would be patentable where Claim 6 was not (Appellant contends that Claim 6 is patentable).

Dependent Claim 12 specifies the method of Claim 11, wherein said external agent comprises estradiol. The cited art, to the extent that it teaches or suggests all of the elements of Claim 11 (Appellant contends that it does not), does not teach an external agent comprising estradiol as claimed in Claim 12. Thus, Claim 12 would be patentable where Claim 11 was not (Appellant contends that Claim 11 is patentable).

Dependent Claim 13 specifies the method of Claim 2, wherein said automated sample handling device comprises a switchable, multi-channel valve. The cited art, to the extent that it teaches or suggests all of the elements of Claim 2 (Appellant contends that it does not), does not teach a switchable, mulit-channel valve as claimed in Claim 13. Thus, Claim 13 would be patentable where Claim 2 was not (Appellant contends that Claim 2 is patentable).

Dependent Claims 15 and 16 stand or fall together and specify (Claim 15) The method of Claim 14, wherein said buffer comprises a compound of the formula n-octyl C_6-C_{12} glycopyranoside and (Claim 16) the method of Claim 15, wherein said compound of the formula n-octyl C_6-C_{12} glycopyranoside is selected from n-octyl ß-D-glucopyranoside and n-octyl ß-D-galactopyranoside. The cited art, to the extent that it teaches or suggests all of the elements of Claim 14 (Appellant contends that it does not), does not teach a a compound of the formula n-octyl C_6-C_{12} glycopyranoside as claimed in Claim 15 or the compound being selected from n-octyl ß-D-glucopyranoside and n-octyl ß-D-galactopyranoside as claimed in Claim 16. Thus, Claims 15 and 16 would be patentable where Claim 14 was not (Appellant contends that Claim 14 is patentable).

Claims 28-32, and 34 stand or fall together. Independent Claim 28 specifies a system for

the production of a data representation of a protein profile map, comprising: a non-porous reverse phase HPLC separating apparatus; an automated sample handling apparatus configured to receive first and second separated protein samples from said reverse phase HPLC separating apparatus; a mass spectroscopy apparatus configured to receive proteins from said automated sample handling apparatus; a processor configured to produce a data representation of a protein profile map for said first and second separated protein samples analyzed by said mass spectroscopy apparatus, wherein said protein profile map displays protein abundance and mass of a separated protein sample, wherein said protein profile map displays proteins as separate bands corresponding to said protein abundance and mass of said separated protein sample, and wherein the intensity of said bands corresponds to the abundance of said proteins, wherein said protein profile maps for each of said first and second samples are displayed side by side; and a display apparatus that displays said protein profile maps.

Dependent Claim 33 specifies the system of Claim 28, wherein said automated sample handling device comprises a switchable, multi-channel valve. The cited art, to the extent that it teaches or suggests all of the elements of Claim 28 (Appellant contends that it does not), does not teach a switchable, mulit-channel valve as claimed in Claim 33. Thus, Claim 33 would be patentable where Claim 28 was not (Appellant contends that Claim 28 is patentable).

Claim 35 and 36 stand or fall together. Independent Claim 35 specifies a method of producing protein profile maps, comprising: providing a first sample comprising a plurality of proteins; a second sample comprising a plurality of proteins; a separating apparatus, wherein said separating apparatus separates proteins based on a physical property; a mass spectroscopy apparatus; and treating said first and second samples with said separating apparatus to produce a first separated protein sample and a second separated protein sample, wherein said first and second separated protein samples are collected from said separating apparatus in a plurality of fractions, each of said fractions defined by a physical property; analyzing said plurality of fractions from each of said first and second separated protein samples with said mass spectroscopy apparatus to produce first and second protein profile maps for each of said first and second protein samples, wherein said protein profile maps display protein abundance and mass of said first protein sample and said second protein sample; and displaying a differential display protein map of said first and second protein profile maps, wherein said differential display

protein map displays the difference in protein abundance versus mass between proteins in said first and second protein samples, and wherein said differential display protein profile map displays the difference in protein abundance between each protein as a separate band corresponding to said mass of said first protein sample and said second protein sample, and wherein the intensity of said band corresponds to the difference in protein abundance.

Dependent Claim 37 specifies the method of claim 36, wherein said first and second protein profile maps and said differential display map are displayed side by side. The cited art, to the extent that it teaches or suggests all of the elements of Claim 36 (Appellant contends that it does not), does not teach side by side display of differential display maps as claimed in Claim 37. Thus, Claim 37 would be patentable where Claim 36 was not (Appellant contends that Claim 36 is patentable).

VIII. ARGUMENT

A. **Issue 1** – Whether Claims 1-6, 8-20, 22-24, and 26-33 are obvious over Chong et al. (Rapid Commun. Mass Spectrometr 12:1986 [1998]); hereinafter Chong) in view of Richmond et al (Richmond et al., J. Chromatography 835:29 [1999]; hereinafter Richmond).

Claims 1-6, 8-20, 22-24 and 26-33 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over the combination of Chong and Richmond. A *prima facie* case of obviousness requires the Office to cite a reference, or combination of references, that (a) discloses all of the elements of the claimed invention, (b) provides a suggestion or motivation to one of skill in the art to combine the elements to yield the claimed combination, and (c) provides a reasonable expectation of successfully carrying out the claimed combination. Failure to establish any one of the three requirements precludes a finding of a *prima facie* case of obviousness, and, without more, entitles the Applicants to allowance of the claims at issue.[1] The Office has failed to establish a *prima facie* case of obviousness because 1) the Office has not provided a motivation to combine the references; 2) the Office is applying hindsight reconstruction; 3) the Office is improperly disregarding the Lubman Declaration; and 4) the cited references do not teach all of the elements of the claimed invention.

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[1] *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990).

1. There Is No Motivation To Combine The References In The Manner Indicated By The Office

The Office fails to provide any proper evidence of a motivation to combine the Richmond and Chong references, thus a *prima facie* case of obviousness has not been established. The Chong reference cited by the Examiner is directed towards protein separation and mass spectrometry methods. However, Chong is silent as to the protein profile maps of the present invention, which are utilized to display properties of separated and mass spectrally analyzed proteins. The Examiner has cited Richmond as teaching the protein profile maps of the present invention. Richmond teaches a mass spectrometry display method but is silent as to analysis and display of proteins.

In particular, the Applicants submit that the Examiner has pointed to no teaching in either Chong or Richmond to combine the references to arrive at the presently claimed invention. For example, Richmond provides no teaching that the display methods that Richmond applies to chemical samples be used in the display of protein samples, let alone multiple protein samples. The Examiner states "Richmond et al., however, states colored computer screen pictures and 3D maps provides quick and easy way of delivering liquid chromatograph (i.e. high performance liquid chromatography/HPLC data to laboratories...." (Office Action mailed 5/18/04, pg. 3). The applicants submit that the above statement does not provide a motivation to combine the teachings of Richmond with the teachings of Chong, as evidenced by the remainder of the sentence (that the Examiner did not quote) "[t]o laboratories in traditional synthetic chemistry, combinatorial chemistry and natural products chemistry." This is in direct contrast to Chong and the present invention, which are directed towards analysis of **proteins** (See e.g., Claim 1).

Furthermore, as the Examiner has admitted (Office Action mailed 5/18/04, pg. 3), Chong does not suggest the need for an alternate display method (*i.e.*, there is no basis in Chong or Richmond that would lead one to even contemplate modification of Chong as suggested by the Examiner).

In response to the Applicant's arguments, the The Office has made the following statements:

> "Thus, it would have been obvious to someone of ordinary skill in the art at the time of the invention practice Chong et al. in view of Richmnd protein profiling of whole cell lysates wherein protein fractions are separated by non-porous reverse

> phase HPLC and analyzed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-FORMS), with Richmond et al., graphical display of color intensity bands represents (intensity/mass) from liquid chromatography information side-by-side. Again, while it is acknowledged Chong et al. does not suggest the need for an alternate display method it is the motivation found in Richmond which provides the combination of these two references since Richmond states colored computer screen pictures and 3D maps provide quick and easy way of delivery liquid chromatography (HPLC) data to laboratories in traditional synthetic chemistry, combinatorial chemistry and natural products chemistry." (Final office action, pg. 4).
>
> "With respect to Applicants assertion Richmond et al. teaches away from a combination with Chong et al., particularly the analysis of proteins would not be conducted in laboratories in traditional synthetic chemistry, combinatorial chemistry and natural products chemistry; is found moot since proteins are known in the art to be chemical compound that are naturally found or can be synthesized." (Final office action, pg. 4-5).

Applicants respectfully submit that these statements are **misapplications of the law**.

The Office's basic argument is that the methods of Richmond could in theory be applied to Chong, that one would be motivated to make the combination. The court have repeatedly stated that this is not the proper standard:

> "Although the Commissioner suggest that [the structure in the primary prior art reference] could readily be modified to form the [claimed] structure, '[t]he mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggest the desirability of the modification.' " *In re Laskowski*, 871 F.2d 115, 10 USPQ2d 1397 (Fed Cir. 1989).
>
> Although a prior art device "may be capable of being modified to run the way [the patent applicant's] apparatus is claimed, there must be a suggestion or motivation in the reference to do so." *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed Cir. 1990)
>
> The Applicants further submit that the Examiner has ignored the Applicants assertion that Richmond and Chong are in unrelated areas of art. The Federal Circuit has stated: "The teachings of the references, their relatedness to the field of the applicant's endeavor, and the knowledge of person of ordinary skill in the filed of the invention, are all relevant considerations...." *In re Dance*, 160 F.3d 1339, 48 USPQ2d 1635 (Fed Cir 1998).

In particular, the Examiner's statement that "proteins are known in the art to be chemical

compound that are naturally found or can be synthesized...." (Final Office Action, pg. 5) is not supported by the law as a valid motivation to modify or combine the references. M.P.E.P. 2141.01(a) states "In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the filed of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the invention was concerned." The Applicants submit the Richmond does not meet the Office's own standard for analogous art and thus is improperly cited by the Examiner.

The Applicants submit that the Examiner has failed to provide the required motivation to combine the teachings of Chong and Richmond. The mere fact that the methods of Richmond could be used in the display of protein separation data does not relieve the Examiner of his burden to provide some motivation from within the teachings of Chong (which the Examiner has admitted does not provide such teaching) and Richmond, which is in an unrelated area of art and does not suggest the use of the disclosed methods with proteins. Nor has the Examiner provided a motivation from the knowledge of a person of ordinary skill in the art. The Applicants request that the Examiner point to a motivation, either from within the teachings, or from one of ordinary skill in the art (e.g., a declaration of one of ordinary skill in the art at the time of filing of the present invention).

The Examiner thus appears to *assume* that such motivation exists in the "general knowledge," without providing any basis for such an assumption. As discussed above, however, the requisite motivation must be found either in the prior art or in knowledge that is generally available to those of ordinary skill in the art; a baseless *assumption* of such knowledge is legally impermissible under *Fine* and *Kotzhab*. Moreover, as the Federal Circuit has held:

> [t]he range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence."

In re Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999) (citations omitted). Since the Examiner has provided no actual evidence to support the conclusory statement that the cited references in combination render the present invention obvious, Applicants respectfully assert that a *prima facie* case of obviousness has not been established.

The Office has also failed to analyze the invention as a whole. When analyzed as a

whole, the display of protein profile maps for separated protein samples is non-obvious. "That each element in a claimed invention is old or unpatentable does not determine the nonobviousness of the claimed invention as a whole." *Custom Accessories v. Jeffrey-Allan Industries Inc.,* 807 F.2d 955, 1 USPQ 2d 1196, 1198 (Fed. Cir. 1986); See also *Brantingson Fishing Equipment Co. v. Shimano American Corp.*, 9 USPQ 2d 1669, 1672 (Fed. Cir. 1988). Put another way: "Only God works from nothing. Men must work with old elements." *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 225 USPQ 26, 31 n. 3 (Fed. Cir. 1985) (quoting from Markey, "Why Not the Statute," 65 JPOS 331, 333-334 (1983)).

The *Fromson* case is particularly relevant here. In that case, the inventor developed a process for photolithography using 1) aluminum as a substrate, 2) oxide coatings by anodization, 3) silication, and 4) application of light-sensitive resins. The district court correctly found that each of these elements individually were known in the art - but incorrectly concluded, on the basis of the unpatentability of each element, that the combination of these steps was unpatentable. On appeal, the Federal Circuit pointed to the "fundamental error" of the district court, noting: "At no point did the court indicate, nor does the record indicate, a basis on which it can be said that the making of that combination would have been obvious when it was made." *Fromson, supra* at 31.

Likewise, in the instant case there has been no showing of why one would be motivated to use the display methods of Richmond in combination with the protein separation methods of Chong. Absent a motivation to combine the references, the Office has not established a prima facie case of obviousness.

2. The Office's Reasoning is Based on Improper Hindsight Reconstruction

The Applicants submit that the Office has improperly applied hindsight reconstruction to combine the Chong and Richmond references. The Examiner has found the alleged motivation to combine the cited references in Applicants' own specification rather than in the cited art or from knowledge within the art. Specifically, to arrive at the presently claimed invention, one of ordinary skill in the art would have had to have been motivated to: **(I)** choose the separation methods of Chong, while ignoring the fact that Chong says nothing about (and, indeed, is not at all concerned with) an alternative display method; and combine these elements with **(II)** the

display method of Richmond, while ignoring the fact that Richmond does not teach or suggest the use of the described methods for display of proteins. Without using the presently claimed invention and the present specification as the blueprint for this hindsight "picking and choosing" of the isolated elements of each reference, one of ordinary skill in the art would have found no specific suggestions to include one element and exclude another from each of the cited references to produce the presently claimed invention. Without such suggestions in the cited art, the combination of the cited references as the Examiner has done is nothing more than a hindsight obviousness analysis.

As the Federal Circuit has held numerous times, however, such a hindsight analysis is impermissible -- instead, the Examiner must show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to make and use the claimed invention. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985) ("When prior art references require selective combination by the [fact-finder] to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself."); *Fine*, 5 USPQ2d at 1600 ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."); *In re Pleuddemann*, 910 F.2d 823, 828 (Fed. Cir. 1990) (noting that use of an applicant's specification as though it were prior art to support an obviousness determination is legal error); *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (holding that both the suggestion to combine references, and a reasonable expectation of success in making the claimed invention, "must be founded in the prior art, not in the applicant's disclosure."). The Board has also provided the same mandate on this issue:

> it is impermissible to use the claimed invention as an instruction manual or "template" to piece together isolated disclosures and teachings of the prior art so that the claimed invention may be rendered obvious . . . . a rejection based on § 103 must rest on a factual basis, with the facts being interpreted without hindsight reconstruction of the invention from the prior art. In making this evaluation, the examiner has the initial duty of supplying the factual basis for the rejection he advances. He may not, because he doubts that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis.

Ex parte Haymond, 41 USPQ2d 1217, 1220 (Bd. Pat. App. Int. 1996). Thus, the use of hindsight analysis in the present case is impermissible and cannot be used to attempt to establish a *prima*

facie case of obviousness. Applicants also are well-aware of the often-cited language in the MPEP that:

> [a]ny judgement [sic] on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper.

MPEP § 2145(X)(A) (quoting *In re McLaughlin*, 443 F.2d 1392, 1395, 170 USPQ 209, 212 (C.C.P.A. 1971)). This boilerplate from the MPEP, however, does not negate the Examiner's burden of providing *specific* evidence or knowledge that would have motivated one of ordinary skill to have modified the cited references and combine their respective disclosures so as to arrive at the presently claimed invention. As noted above, such specific evidence or knowledge has not been provided by the Examiner; hence, the boilerplate language from the MPEP is of no avail in the present case.

Moreover, it is axiomatic that, in order to support a *prima facie* case of obviousness, the prior art must suggest making the *specific* modifications necessary to achieve the claimed invention. *See In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995); *In re Lalu*, 747 F.2d 703, 705 (Fed. Cir. 1984) ("[t]he prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). That is, simply because "one can conceive a general process in advance for generating an *undefined* method [*e.g.*, separating, proteins, and displaying proteins] does not mean that a claimed *specific* method [*e.g.*, the specific methods of the presently claimed invention] was precisely envisioned and therefore obvious." *Deuel* at 1559. Thus, in order for Chong and Richmond to be suitable as primary references upon which to base a *prima facie* case of obviousness, there must be, at a minimum, a teaching or suggestion in these references or in the art that would have compelled one of ordinary skill in the art to include all of the elements of the presently claimed invention in the combination of the presently claimed invention. As noted above, such a teaching or suggestion is wholly lacking in Chong and Richmond. Therefore, the cited references taken together are seriously deficient (particularly in view of the holding in *Deuel*), and cannot support a *prima facie* case of obviousness.

3. The Office Has Improperly Failed to Consider the Lubman Declaration

Applicants **have provided evidence** as to why one skilled in the relevant art would not have been motivated to combine Chong and Richmond to arrive at the presently claimed invention in the form of a declaration by Dr. Lubman. The Office, however, has ignored the evidence presented by the Applicants. In particular, in reference to the patentability of the claims, the Office stated:

> "That is the expert opinion by David M. Lubman fails to set forth facts that the cited prior art does not include, for example..." (Final Office Action, pg. 7)
>
> "Dr. David Lubman provided an expert opinion of claim elements supposedly not found in the cited reference without any explanation as to why such claim elements are considered to be absent in view of the Examiner's cited portion of said elements in the references." (Advisory Action mailed 3/3/05)

Applicants first note that this statement ignores the factual statements of Dr. Lubman's declaration. The office has asked Dr. Lubman to conduct an impossible exercise, that is, to provide factual support for an element **not** found in a reference. It is not possible to provide facts in the reference that support the absence of an element in the reference. This is analogous to requiring that the reference specifically point out what it **does not** teach. This is not the proper standard for rebuttal evidence. The Office provided no legal authority on this point, nor are the Applicants aware of any such legal precedent.

The Office has also failed to respond to Dr. Lubman's statements regarding the lack of motivation to combine Chong and Richmond to arrive at the present claimed invention. Thus, the Office's attempt to claim that the cited references provide a motivation to combine the references to arrive at the presently claimed invention is refuted by Dr. Lubman's declaration, the only actual evidence in the record on this point, which the Office has ignored.

In particular, the Examiner has failed to respond to the following statements by Dr. Lubman regarding the lack of motivation of one skilled in the art to combine the cited references:

16. The Richmond reference is in the field of chemical analysis.
17. The Richmond reference would not have been consulted by someone

> working in the field of protein separation and analysis to solve problems in protein display, as this reference is in a different field and has no bearing on protein analysis.
> 18. There is no scientific basis in any of the references cited by the Examiner that would lead someone to apply the display methods of Richmond to the methods of Chong.

The Office failed to address any of the points listed above. The Federal Circuit has stated time and time again that rebuttal evidence of one skilled in the art cannot be dismissed by the Office without consideration. The Examiner must respond to all of the arguments and evidence presented by Applicants. The MPEP states that:

> **Office personnel should consider all rebuttal arguments and evidence presented by applicants**. . . . *In re Beattie*, 974 F.2d 1309, 1313, 24 USPQ2d 1040, 1042-43 (Fed. Cir. 1992). . . . **Office personnel should avoid giving evidence no weight**, except in rare circumstances. *Id. See also In re Alton*, 76 F.3d 1168, 1174-75, 37 USPQ2d 1578, 1582-83 (Fed. Cir. 1996).
> * * *
> A determination under 35 U.S.C. 103 should rest on **all the evidence** and should not be influenced by any earlier conclusion. *See, e.g., Piasecki*, 745 F.2d at 1472-73, 223 USPQ at 788; *In re Eli Lilly & Co.*, 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990). Thus, once the applicant has presented rebuttal evidence, Office personnel should **reconsider** any initial obviousness determination in view of the entire record. *See, e.g., Piasecki*, 745 F.2d at 1472, 223 USPQ at 788; *Eli Lilly*, 902 F.2d at 945, 14 USPQ2d at 1743.[2]

Additionally, the Courts have held as follows:

> When *prima facie* obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over . . . . An earlier decision should not . . . be considered as set in concrete, and applicant's rebuttal evidence then be evaluated only its knockdown ability. Analytical fixation on an earlier decision can tend to provide the decision with an undeservedly broadened umbrella effect. *Prima facie* obviousness is a legal conclusion, not a fact. Facts established by rebuttal evidence must be evaluated along with the facts on which the earlier conclusion was reached, not against the conclusion itself. Though the tribunal must begin anew, a final finding of obviousness may of course be reached, but such finding will rest upon evaluation of all facts in evidence, uninfluenced by

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[2] MPEP §§2144.08; emphasis added).

> any earlier conclusion reached . . . upon a different record.[3]

Furthermore:

> If a *prima facie* case is made in the first instance, and if the applicant comes forward with a reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed.[4]

Accordingly, even if the Office had established a *prima facie* of obviousness in a preceding office action (and Applicants contend that it did not), the Examiner must respond to Applicants arguments. The failure to properly and factually rebut either the arguments or the evidence advanced by the Applicants is reversible error under *In re Alton*, 76 F.3d 1168, 37 U.S.P.Q.2d 1578 (Fed. Cir. 1996).

In *In re Alton*, the applicants submitted a declaration in order to rebut a *prima facie* case of inadequate written description by the Board of Appeals in an earlier appeal. *Id.* at 1173. Instead of addressing the arguments presented in the declaration, the Examiner dismissed the declaration as opinion evidence that was entitled to little weight. *Id.* at 1173-745. The Federal Circuit remanded the case to the Board, holding that the Board committed error in both viewing the declaration as opinion evidence and dismissing the declaration "without an adequate explanation of why the declaration failed to rebut the Board's *prima facie* case" of unpatentability. Id. at 1174. These bases for reversal were independent. With respect to failure to provide an adequate explanation of why the declaration failed to rebut the *prima facie* case, the Federal Circuit found that:

> In sum, the examiner dismissed the Wall declaration and provided only conclusory statements as to why the declaration did not show that a person skilled in the art would realize that Alton had possession of the claimed subject matter in 1983.

Id. at 1176. In particular, the Federal Circuit held that the examiner failed to address specific points made in the declaration concerning modifications of the amino acids sequence of protein. *Id.*

In re Alton is directly applicable to the present facts. Instead of addressing the arguments

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[3] *In re Rinehart*, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (CCPA 1976).

[4] *In re Hedges*, 783 F.2d 1038, 1039, 228 USPQ 685, 686 (Fed. Cir. 1986).

presented in the Lubman Declaration, the Office has provided only conclusory statements and failed to address the particular evidence offered in the Declaration. As a result, Applicants respectfully request that the Examiner reconsider the evidence offered in the Lubman Declaration. This evidence establishes that cited references cannot be properly combined and thus rebuts a prima facie case of obviousness (which had not been properly established in the first place). Accordingly, Applicants respectfully request that the rejection be withdrawn.

4. The cited references do not teach all of the elements of the presently claimed invention

The Applicants further submit that even if Chong and Richmond are improperly combined, they do not teach all of the elements of the presently claimed invention. In particular, neither Chong nor Richmond, alone or in combination, teach the claim element of a protein profile map that displays protein abundance and mass of a separated protein sample. In addition, neither Chong nor Richmond, even if the teachings of the two references are improperly combined, provide a teaching of a side by side display showing both protein mass and abundance of multiple samples. In rebuttal, the Examiner states "Chong et al. depict the protein profile maps side-by-side in Figure 1..." (Office Action, pg. 4). The applicants respectfully disagree, as the evidence shows otherwise. Figure 1 of Chong does not display a protein profile map "wherein said protein profile maps displays each protein as a **separate band** corresponding to said mass of said first protein sample and said second protein sample, and wherein the **intensity of said band corresponds to said protein abundance** of said first protein sample and said second protein sample." (Claim 1).

Claim 1: "A method of producing protein profile maps, comprising:

a) providing:

i) a first sample comprising a plurality of proteins;

ii) a second sample comprising a plurality of proteins;

iii) a separating apparatus, wherein said separating apparatus separates proteins based on a physical property;

iv) a mass spectroscopy apparatus; and

b) treating said first and second samples with said separating apparatus to

produce a first separated protein sample and a second separated protein sample, wherein said first and second separated protein samples are collected from said separating apparatus in a plurality of fractions, each of said fractions defined by a physical property; and

c) analyzing said plurality of fractions from each of said first and second separated protein samples with said mass spectroscopy apparatus to produce a protein profile map for each of said first and second samples, wherein said protein profile maps display protein abundance and mass of said first protein sample and said second protein sample, and wherein said protein profile maps displays each protein as a separate band corresponding to said mass of said first protein sample and said second protein sample, and wherein the intensity of said band corresponds to said protein abundance of said first protein sample and said second protein sample; and wherein said protein profile maps for each of said first and second samples are displayed side by side."

The Examiner responds "Chong et al. teaches: 1) the depiction of protein profile maps side-by-side in Figure 1, wherein the protein samples are separated and are indicative of protein abundance (intensity)...." (Final Office Action, pg. 3). The Applicants respectfully disagree. The Examiner has pointed to no evidence in Chong (nor is their any) that intensity is correlated with mass. Nor does Chong provide protein profile maps that display each protein as a separate band. Richmond further does not teach this element. The Examiner has pointed to no teachings in Chong or Richmond, alone or in combination teach a protein profile map "wherein said protein profile maps displays each protein as a **separate band** corresponding to said mass of said first protein sample and said second protein sample, and wherein the **intensity of said band corresponds to said protein abundance** of said first protein sample and said second protein sample."

Furthermore, the Examiner has pointed to no teaching in Chong or Richmond, alone or in combination, of the elements of dependent claims 13 or 21. For example, the Examiner has pointed to no teaching (nor is any present) in Chong or Richmond of the claim element of a switchable, multichannel valve (Claims 13 and 33).

Claim 13: "The method of Claim 2, wherein said automated sample handling device comprises a switchable, multi-channel valve."

Claim 33: "The system of Claim 28, wherein said automated sample handling device comprises a switchable, multi-channel valve."

In rebuttal, the Examiner states "Chong et al. utilize the Beckman System Gold HPLC having a programmable solvent delivery module with a dual pump (switchable, multichannel valve)...." (Office Action mailed 5/18/04, pg. 4). The applicants respectfully disagree and submit that the Examiner has improperly characterized "switchable, multichannel valve" and direct the Examiner to the Applicants' definition:

> "A switchable multi-channel valve allows multiple apparatus to be connected to one automated sample handler. For example, sample can first be directed through one apparatus of a system (*e.g.*, a first chromatography apparatus). The sample can then be directed through a different channel of the valve to a second apparatus (*e.g.*, a second chromatography apparatus). " Specification, pg. 14, lines 8-12.

In the advisory action mailed 3/3/05, the Examiner simply reiterates his previous argument without rebutting the Applicants arguments. In particular, the Examiner states:

> "[u]tilizes the Beckman System Gold HPLC which has a programmable solvent delivery module with a dual pump (switchable, multichannel valve), further the System Control Center permits the control of the pump and external modules directly (additionally pumps, therefore, multi-channel valve)." (Final Office action mailed 11/17/05, pg. 3).

The Applicants submit that not only has the Examiner failed to refute the Applicants arguments that a pump on the same instrument (e.g., HPLC) is the "second apparatus" explicitly stated in the Specification, the Examiners example of an "additional pump" directly supports the Applicants argument that a dual pump on an HPLC is not a switchable, multichannel valve. As such, the Applicants submit that neither Chong, nor Richmond, alone or in combination, teach the claim element of a switchable, multichannel valve for use in delivering sample from one apparatus to another.

The Examiner continues to cite the dual pump system described in Chong as a "switchable, multichannel valve" without pointing to specific support for a valve that allows **multiple apparatuses** to be connected to **one sample handler.** Verentchikov further does not teach such a valve. As such, the Applicants submit that neither Chong, nor Richmond, alone or in combination, teach the claim element of a switchable, multichannel valve for use in delivering sample from one apparatus to another.

In addition, neither Chong, nor Richmond, alone or in combination teach the claim

elements of an automated sample handling device that transfers first and second samples from said separating apparatus to said mass spectrometry apparatus (Claim 2):

Claim 2: "The method of Claim 1, further comprising an automated sample handling device operably linked to said separating apparatus and said mass spectroscopy apparatus, wherein said sample handling device transfers said first and second samples to said separating apparatus, and wherein said sample handling device transfers said first and second separated protein samples from said separating apparatus to said mass spectroscopy apparatus."

Furthermore, neither Chong, nor Richmond, alone or in combination, teach the claim elements of a centralized control network operably linked to the automated sample handling device, wherein said centralized control network controls the operations of said automated sample handling device, said separating apparatus, and said mass spectroscopy apparatus (Claim 3) or the centralized control network comprising computer memory and a computer processor:

Claim 3: "The method of Claim 2, further comprising a centralized control network operably linked to said automated sample handling device, said separating apparatus, and said mass spectroscopy apparatus, wherein said centralized control network controls the operations of said automated sample handling device, said separating apparatus, and said mass spectroscopy apparatus."

Claim 4: "The method of Claim 3, wherein said centralized control network comprises computer memory and a computer processor."

Additionally, neither Chong, nor Richmond, alone or in combination, teach the claim elements of treating a sample with an external agent prior to treating the samples to the separating apparatus, wherein the external agent is estradiol (Claim 12):

Claim 12 "The method of Claim 11, wherein said external agent comprises estradiol."

In addition, neither Chong, nor Richmond, alone or in combination, teach the claim elements of a buffer comprising the formula n-octyl C_6-C_{12} glycopyranoside (Claim 15) or the buffer being selected from the formula n-octyl ß-D-glucopyranoside and n-octyl ß-D-galactopyranoside (Claim 16):

Claim 15: "The method of Claim 14, wherein said buffer comprises a compound of the formula n-octyl C_6-C_{12} glycopyranoside."

Claim 16: "The method of Claim 15, wherein said compound of the formula n-octyl C_6-

C_{12} glycopyranoside is selected from n-octyl ß-D-glucopyranoside and n-octyl ß-D-galactopyranoside."

The Examiner has pointed to no teaching in Chong or Richmond, alone or in combination of the above claim elements.

The Court of Appeals for the Federal Circuit sets forth the Examiner's obligation as follows:

> "In determining obviousness, the invention must be considered as a whole without the benefit of hindsight, and the claims must be considered in their entirety."[5]

To the contrary, the Appellant contends that the Examiner has manifestly not considered the claims of the present invention in their entirety, and has not considered the invention as a whole. Despite having engaged in far-reaching hindsight analysis (discussed above), the Examiner has nevertheless failed to identify all of the elements of the presently claimed invention in the prior art. As a consequence, the Examiner's cited references do not remedy one another's defects in combination. In view of the above, the Appellant respectfully requests that the rejection be withdrawn.

Issue 2 – Whether Claims 35-37 are obvious light of Chong taken in view of Richmond and further in view of Pandey et al. (Nature 405: 837 (2000); hereinafter Pandey).

Claims 35-37 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over the combination of Chong, Richmond, and Pandey. The Office has failed to establish a *prima facie* case of obviousness because 1) the Office has not provided a motivation to combine the references; 2) the Office is applying hindsight reconstruction; 3) the Office is improperly disregarding the Lubman Declaration; and 4) the cited references do not teach all of the elements of the claimed invention.

1. There Is No Motivation To Combine The References In The Manner Indicated By The Office

The Office fails to provide suitable evidence of a motivation to combine the Richmond, Chong, and Pandey references, thus a *prima facie* case of obviousness has not been established.

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5 *Rockwell International Corp. v. United States*, 147 F.3d 1358, 47 USPQ2d 1027 (Fed. Cir. 1998).

In particular, the Applicants submit that the Examiner has pointed to no teaching in either Chong, Pandey or Richmond to combine the references to arrive at the presently claimed invention. Claims 35-37 are directed towards differential display methods of comparing protein profile maps.

As described above, the Office has failed to demonstrate a motivation to combine the teachings of Chong and Richmond. The Office has further failed to provide a motivation to combine Pandey with Chong and Richmond. The Office states "Chong et al. taken in view of Richmond et al. is herein applied as above and from the previous office action, mailed 01 October 2003. However, Chong et al. and/or Richmond et al. fail to utilize differential display to depict protein profile maps." (Office Action mailed 5/18/05, pg. 5). The Office cites Pandey as teaching this limitation. In particular, the Office has stated: "Since Pandey et al. describes the application of differential display in the field of proteomics, particularly mass spectrometry protein profile maps." (pg. 5, Office Action, mailed 5/18/05).

Indeed, the Pandey reference reviews the current state of the art in proteomics at the time the reference was published and does not point to any deficiencies in techniques used for mass spectrum display. Nor does Pandey suggest any need in the art for alternative mass spectrum display methods. The Applicants remind the Examiner of his obligation to specifically point out such teaching.

The Examiner responds: "Since Pandey et al. describes the application of differential display in the field of proteomics, particularly mass spectrometry protein profile maps for a more faster, more convenient, and more comprehensive analysis of protein." (Final Office Action, pg. 6).

As described above, the examiner has misapplied the law (See above discussion of relevant Federal Circuit cases). The mere existence of differential display techniques does not provide a motivation to combine the techniques with the teachings of Chong and Richmond, particularly given the fact that neither Chong nor Richmond suggest the use of differential display and Pandey does not suggest the need for additional display methods. The above statement by the Examiner actually supports the Applicants' position in that Pandey teaches that the state of the art provides satisfactory methods for analysis of proteins.

Since the Examiner has provided no actual evidence to support the conclusory statement

that the cited references in combination render the present invention obvious, and there has been no showing of why one would be motivated to use the display methods of Richmond in combination with the protein separation methods of Chong and the review of Pandey. Absent a motivation to combine the references, the Office has not established a prima facie case of obviousness.

2. The Office's Reasoning Demonstrates Hindsight Reconstruction

The Applicants submit that the Office has improperly applied hindsight reconstruction to combine the Chong, Richmond, and Pandey references. The Examiner has found the alleged motivation to combine the cited references in Applicants' own specification rather than in the cited art or from knowledge within the art. Specifically, to arrive at the presently claimed invention, one of ordinary skill in the art would have had to have been motivated to: **(I)** choose the separation methods of Chong, while ignoring the fact that Chong says nothing about (and, indeed, is not at all concerned with) an alternative display method; and combine these elements with **(II)** the display method of Richmond, while ignoring the fact that Richmond does not teach or suggest the use of the described methods for display of proteins; and **(III)** the generic review language of Pandey indicating no need for additional display methods. Without using the presently claimed invention and the present specification as the blueprint for this hindsight picking and choosing the isolated elements of each reference, one of ordinary skill in the art would have found no specific suggestions to include one element and exclude another from each of the cited references to produce the presently claimed invention. Without such suggestions in the cited art, the combination of the cited references as the Examiner has done is nothing more than a hindsight obviousness analysis.

As the Federal Circuit has held numerous times, however, such a hindsight analysis is impermissible (See above citations and discussion of the appropriate law)-- instead, the Examiner must show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to make and use the claimed invention.

3. The Office Has Improperly Failed to Consider the Lubman Declaration

Applicants **have provided evidence** as to why one skilled in the relevant art would not have been motivated to combine Chong and Richmond to arrive at the presently claimed invention in the form of a declaration by Dr. Lubman. The Office, however, has ignored the evidence presented by the Applicants. In particular, in reference to the patentability of the claims, the Office stated:

> "That is the expert opinion by David M. Lubman fails to set forth facts that the cited prior art does not include, for example..." (Final Office Action, pg. 7)
>
> "Dr. David Lubman provided an expert opinion of claim elements supposedly not found in the cited reference without any explanation as to why such claim elements are considered to be absent in view of the Examiner's cited portion of said elements in the references." (Advisory Action mailed 3/3/05)

Applicants first note that this statement ignores the factual statements of Dr. Lubman's declaration. The office has asked Dr. Lubman to conduct an impossible exercise, that is, to provide factual support for an element **not** found in a reference. It is not possible to provide facts in the reference that support the absence of an element in the reference. This is analogous to requiring that the reference specifically point out what it **does not** teach. This is not the proper standard for rebuttal evidence. The Office provided no legal authority on this point, nor are the Applicants aware of any such legal precedent.

The Office has also failed to respond to Dr. Lubman's statements regarding the lack of motivation to combine Chong, Richmond and Pandey to arrive at the present claimed invention. Thus, the Office's attempt to claim that the cited references provide a motivation to combine the references to arrive at the presently claimed invention is refuted by Dr. Lubman's declaration, which the Office has ignored.

In particular, the Examiner has failed to respond to the following statements by Dr. Lubman regarding the lack of motivation of one skilled in the art to combine the cited references:

24. The Pandey references teaches standard methods of mass spectrum display that would have been used by someone working in the field of protein separation and analysis at the time the reference was published.

25. The Pandey reference does not describe deficiencies in the methods of displaying mass spectrum that were used at the time the reference was published.

26. The Pandey reference does not describe a need for alternative methods for the

display of mass spectrum. Therefore, a scientist reading the Pandey reference would have no particular motivation to alter the display method or use different display methods.

27. There is no scientific basis in any of the references cited by the Examiner that would lead someone to apply the display methods of Richmond to the methods of Pandey.

The Office fails to address any of the points listed above. The Federal Circuit has stated time and time again that rebuttal evidence of one skilled in the art can not be dismissed by the Office without consideration (See above citations of case law). The Examiner must respond to all of the arguments and evidence presented by Applicants.

Accordingly, even if the Office had established a *prima facie* of obviousness in a preceding office action (and Applicants contend that it did not), the Examiner must respond to Applicants' arguments. The failure to properly and factually rebut either the arguments or the evidence advanced by the Applicants is reversible error under *In re Alton*, 76 F.3d 1168, 37 U.S.P.Q.2d 1578 (Fed. Cir. 1996). Instead of addressing the arguments presented in the Lubman Declaration, the Office has provided only conclusory statements and failed to address the particular evidence offered in the Declaration. As a result, Applicants respectfully request that the Examiner reconsider the evidence offered in the Lubman Declaration. This evidence establishes that cited references cannot be properly combined and thus rebuts a prima facie case of obviousness. Accordingly, Applicants respectfully request that the claims be passed to allowance.

4. The cited references do not teach all of the elements of the presently claimed invention

The Applicants further submit that even if Chong, Richmond and Pandey are improperly combined, they do not teach all of the elements of the presently claimed invention.

The Examiner states "However, Chong et al. and/or Richmond et al. fail to utilize differential display to depict protein profile maps." (Office Action, pg. 5). The Examiner then cites Pandey to overcome this deficiency. The Applicants respectfully disagree and submit that Pandey does not teach this element of the claims alone or in combination with Chong and/or Richmond (See above discussion of the deficiencies in Chong and Richmond). The Examiner states "The process of applying differential display to mass spectrometry data is described and

illustrated...." (Final Office Action, pg. 5). The applicants respectfully disagree and submit that neither Figures 1 and 3 (nor any teaching in Pandey, alone or in combination with Chong and/or Richmond) do not teach the claim element of "wherein said differential display protein profile map displays the difference in protein abundance between each protein as a **separate band** corresponding to said mass of said first protein sample and said second protein sample, and wherein the **intensity** of said band corresponds to the difference in protein abundance." (Claim 35).

The Court of Appeals for the Federal Circuit sets forth the Examiner's obligation as follows:

> "In determining obviousness, the invention must be considered as a whole without the benefit of hindsight, and the claims must be considered in their entirety."[6]

To the contrary, the Appellant contends that the Examiner has manifestly not considered the claims of the present invention in their entirety, and has not considered the invention as a whole. Despite having engaged in far-reaching hindsight analysis (discussed above), the Examiner has nevertheless failed to identify all of the elements of the presently claimed invention in the prior art. As a consequence, the Examiner's cited references do not remedy one another's defects in combination. In view of the above, the Appellant respectfully requests that the rejection be withdrawn.

Issue 3 - Whether Claims 1-6, 8-24 and 26-34 are obvious in light of Chong taken in view of Richmond and further in view of Verentchikov (U.S. Patent 6,534,764; hereinafter Verentchikov).

Claims 1-6, 8-24, and 26-34 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over the combination of Chong, Richmond, and Verentchikov. The Office has failed to establish a *prima facie* case of obviousness because 1) the Office has not provided a motivation to combine the references; 2) the Office is applying hindsight reconstruction; and 3) the cited references do not teach all of the elements of the claimed invention.

1. There Is No Motivation To Combine The References In The Manner

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6 *Rockwell International Corp. v. United States*, 147 F.3d 1358, 47 USPQ2d 1027 (Fed. Cir. 1998).

Indicated By The Office

The Office fails to provide suitable evidence of a motivation to combine the Richmond, Chong, and Verentchikov references, thus a *prima facie* case of obviousness has not been established. In particular, the Applicants submit that the Examiner has pointed to no teaching in either Chong, Verentchikov or Richmond to combine the references to arrive at the presently claimed invention.

As described above, the Office has failed to demonstrate a motivation to combine the teachings of Chong and Richmond. The Office has stated "Chong et al. taken in view of Richmond et al. is herein applied as above and from the previous office actions. However, neither reference teaches the specific utilization of electronspray ionization-orthogonal acceleration-time -of-flight mass spectrometry." The Examiner cites Verentchikov as providing this element of the claims. However, Verentchikov further provides no motivation to combine Chong and Richmond. In particular, as the Examiner has admitted (Final Office Action, pg. 6), Verentchikov does not teach or suggest the application of the described mass spectrometry techniques to the analysis of proteins.

The Office has stated: "Generic samples are described, however, peptide samples are clearly given a reasonable expectation of success in such practice." (pg. 6, Final Office Action). The Applicants respectfully disagree and submit that the Examiner has misapplied the law (See above discussion of relevant Federal Circuit decisions). The Examiner is required under the law to specifically point out where the motivation to combine the references is within the references. Generic, conclusory statement regarding the state of the art are not permitted (See above discussion of the relevant law). The mere existence of esi-TOF mass spectrometry does not provide a motivation to apply such methods to use with the systems described by Chong and Richmond. The Applicants remind the Examiner of his obligation to specifically point out such teaching.

Since the Examiner has provided no actual evidence to support the conclusory statement that the cited references in combination render the present invention obvious, Applicants respectfully assert that a *prima facie* case of obviousness has not been established.

2. The Office's Reasoning Demonstrates Hindsight Reconstruction

The Applicants submit that the Office has improperly applied hindsight reconstruction to combine the Chong and Richmond references. The Examiner has found the alleged motivation to combine the cited references in Applicants' own specification rather than in the cited art or from knowledge within the art. Specifically, to arrive at the presently claimed invention, one of ordinary skill in the art would have had to have been motivated to: **(I)** choose the separation methods of Chong, while ignoring the fact that Chong says nothing about (and, indeed, is not at all concerned with) an alternative display method; and combine these elements with **(II)** the display method of Richmond, while ignoring the fact that Richmond does not teach or suggest the use of the described methods for display of proteins; and **(III)** the generic description lacking application to proteins of Verentchikov. Without using the presently claimed invention and the present specification as the blueprint for this hindsight picking and choosing the isolated elements of each reference, one of ordinary skill in the art would have found no specific suggestions to include one element and exclude another from each of the cited references to produce the presently claimed invention. Without such suggestions in the cited art, the combination of the cited references as the Examiner has done is nothing more than a hindsight obviousness analysis.

As the Federal Circuit has held numerous times, however, such a hindsight analysis is impermissible (See above citations and discussion of the appropriate law)-- instead, the Examiner must show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to make and use the claimed invention.

3. The cited references do not teach all of the elements of the presently claimed invention

The Applicants further submit that even if Chong, Richmond and Verentchikov are improperly combined, they do not teach all of the elements of the presently claimed invention. In particular, neither Chong nor Richmond nor Verentchikov, alone or in combination, teach the claim element of "wherein said protein profile maps displays each protein as a **separate band** corresponding to said mass of said first protein sample and said second protein sample, and wherein the **intensity of said band corresponds to said protein abundance** of said first protein sample and said second protein sample." In addition, neither Chong nor Richmond nor

Verentchikov, even if the teachings of the two references are improperly combined, provide a teaching of a **side by side** display showing **both** protein mass and abundance of multiple samples. The Examiner has failed to point to any teachings in any of the cited references of these elements.

Furthermore, the Examiner has pointed to no teaching in Chong, Verentchikov, or Richmond, alone or in combination, of the elements of dependent claims 13 or 21. For example, the Examiner has pointed to no teaching (nor is any present) in Chong or Richmond of the claim element of a switchable, multichannel valve (Claims 13 and 33).

Claim 13: "The method of Claim 2, wherein said automated sample handling device comprises a switchable, multi-channel valve."

Claim 33: "The system of Claim 28, wherein said automated sample handling device comprises a switchable, multi-channel valve."

The Applicant's response to the Examiner's continued incorrect statements that Chong and Richmond teach a switchable, multichannel valve is provided above. The Examiner has pointed to not teaching in Verentchikov of this elements, nor does Verentchikov teach this element.

In addition, neither Chong, Verentchikov, nor Richmond, alone or in combination teach the claim elements of an automated sample handling device that transfers first and second samples from said separating apparatus to said mass spectrometry apparatus (Claim 2):

Claim 2: "The method of Claim 1, further comprising an automated sample handling device operably linked to said separating apparatus and said mass spectroscopy apparatus, wherein said sample handling device transfers said first and second samples to said separating apparatus, and wherein said sample handling device transfers said first and second separated protein samples from said separating apparatus to said mass spectroscopy apparatus."

Furthermore, neither Chong, Verentchikov, nor Richmond, alone or in combination, teach the claim elements of a centralized control network operably linked to the automated sample handling device, wherein said centralized control network controls the operations of said automated sample handling device, said separating apparatus, and said mass spectroscopy apparatus (Claim 3) or the centralized control network comprising computer memory and a computer processor:

Claim 3: "The method of Claim 2, further comprising a centralized control network operably linked to said automated sample handling device, said separating apparatus, and said mass spectroscopy apparatus, wherein said centralized control network controls the operations of said automated sample handling device, said separating apparatus, and said mass spectroscopy apparatus."

Claim 4: "The method of Claim 3, wherein said centralized control network comprises computer memory and a computer processor."

Additionally, neither Chong, Verentchikov, nor Richmond, alone or in combination, teach the claim elements of treating a sample with an external agent prior to treating the samples to the separating apparatus, wherein the external agent is estradiol (Claim 12):

Claim 12 "The method of Claim 11, wherein said external agent comprises estradiol."

In addition, neither Chong, Verentchikov, nor Richmond, alone or in combination, teach the claim elements of a buffer comprising the formula n-octyl C_6-C_{12} glycopyranoside (Claim 15) or the buffer being selected from the formula n-octyl ß-D-glucopyranoside and n-octyl ß-D-galactopyranoside (Claim 16):

Claim 15: "The method of Claim 14, wherein said buffer comprises a compound of the formula n-octyl C_6-C_{12} glycopyranoside."

Claim 16: "The method of Claim 15, wherein said compound of the formula n-octyl C_6-C_{12} glycopyranoside is selected from n-octyl ß-D-glucopyranoside and n-octyl ß-D-galactopyranoside."

The Examiner has pointed to no teaching in Chong, Verentchikov or Richmond, alone or in combination of the above claim elements.

The Court of Appeals for the Federal Circuit sets forth the Examiner's obligation as follows:

> "In determining obviousness, the invention must be considered as a whole without the benefit of hindsight, and the claims must be considered in their entirety."[7]

To the contrary, the Appellant contends that the Examiner has manifestly not considered the claims of the present invention in their entirety, and has not considered the invention as a whole. Despite having engaged in far-reaching hindsight analysis (discussed above), the Examiner has

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[7] *Rockwell International Corp. v. United States*, 147 F.3d 1358, 47 USPQ2d 1027 (Fed. Cir. 1998).

nevertheless failed to identify all of the elements of the presently claimed invention in the prior art. As a consequence, the Examiner's cited references do not remedy one another's defects in combination. In view of the above, the Appellant respectfully requests that the rejection be withdrawn.

C. Conclusion

For the foregoing reasons, it is submitted that the Office's rejection of Claims 1-6, 8-24, and 26-37 was erroneous, and reversal of the rejections is respectfully requested. Appellant requests either that the Board render a decision as to the allowability of the claims, or alternatively, that the application be remanded for reconsideration by the Office.

Dated: June 20, 2005

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APPENDIX A

CLEAN VERSION OF THE ENTIRE SET OF PENDING CLAIMS

1. (previously presented) A method of producing protein profile maps, comprising:

a) providing:

i) a first sample comprising a plurality of proteins;

ii) a second sample comprising a plurality of proteins;

iii) a separating apparatus, wherein said separating apparatus separates proteins based on a physical property;

iv) a mass spectroscopy apparatus; and

b) treating said first and second samples with said separating apparatus to produce a first separated protein sample and a second separated protein sample, wherein said first and second separated protein samples are collected from said separating apparatus in a plurality of fractions, each of said fractions defined by a physical property; and

c) analyzing said plurality of fractions from each of said first and second separated protein samples with said mass spectroscopy apparatus to produce a protein profile map for each of said first and second samples, wherein said protein profile maps display protein abundance and mass of said first protein sample and said second protein sample, and wherein said protein profile maps displays each protein as a separate band corresponding to said mass of said first protein sample and said second protein sample, and wherein the intensity of said band corresponds to said protein abundance of said first protein sample and said second protein sample; and wherein said protein profile maps for each of said first and second samples are displayed side by side.

2. (original) The method of Claim 1, further comprising an automated sample handling device operably linked to said separating apparatus and said mass spectroscopy apparatus, wherein said sample handling device transfers said first and second samples to said separating apparatus, and wherein said sample handling device transfers said first and second separated

protein samples from said separating apparatus to said mass spectroscopy apparatus.

3. (original) The method of Claim 2, further comprising a centralized control network operably linked to said automated sample handling device, said separating apparatus, and said mass spectroscopy apparatus, wherein said centralized control network controls the operations of said automated sample handling device, said separating apparatus, and said mass spectroscopy apparatus.

4. (original) The method of Claim 3, wherein said centralized control network comprises computer memory and a computer processor.

5. (original) The method of Claim 1, wherein said first sample comprises a cell lysate from a first cell type and said second sample comprises a cell lysate from second cell type.

6. (original) The method of Claim 5, wherein said first cell type is a cancerous cell type and said second cell type is a non-cancerous cell type.

7. (canceled)

8. (previously presented) The method of Claim 1, wherein said bands are bands of different colors.

9. (original) The method of Claim 1, wherein said protein abundance and mass are indicative of the cell type of said protein sample.

10. (original) The method of Claim 1, further comprising the step of d) determining the identity of individual bands on said protein profile map.

11. (original) The method of Claim 6, further comprising the step of treating said first sample with an external agent prior to treating said first and second samples with said separating

apparatus.

12. (original) The method of Claim 11, wherein said external agent comprises estradiol.

13. (original) The method of Claim 2, wherein said automated sample handling device comprises a switchable, multi-channel valve.

14. (original) The method of Claim 1, wherein said first and second samples further comprise a buffer, wherein said plurality of proteins are solubilized in said buffer and wherein said buffer is compatible with said separating apparatus and said mass spectroscopy apparatus.

15. (previously presented) The method of Claim 14, wherein said buffer comprises a compound of the formula n-octyl C_6-C_{12} glycopyranoside.

16. (original) The method of Claim 15, wherein said compound of the formula n-octyl C_6-C_{12} glycopyranoside is selected from n-octyl ß-D-glucopyranoside and n-octyl ß-D-galactopyranoside.

17. (original) The method of Claim 1, wherein said separating apparatus comprises a liquid phase separating apparatus.

18. (original) The method of Claim 17, wherein said liquid phase separating apparatus comprises a reverse phase HPLC separating apparatus.

19. (original) The method of Claim 18, wherein said reverse phase HPLC comprises non-porous reverse phase HPLC.

20. (original) The method of Claim 1, wherein prior to said analyzing said first and second separated protein samples by mass spectroscopy, said first and second samples are divided into first and second portions and wherein said second portions are subjected to

enzymatic digestion.

21. (previously presented) The method of Claim 1, wherein said analyzing said first and second separated protein samples by mass spectrometry comprises analyzing said samples by electrospray ionization-orthogonal acceleration-time-of-flight mass spectrometry.

22. (original) The method of Claim 1, wherein said analyzing said first and second separated protein samples by mass spectrometry comprises analyzing said samples by a technique selected from the group consisting of ion trap mass spectrometry, ion trap/time-of-flight mass spectrometry, quadrupole and triple quadrupole mass spectrometry, Fourier Transform (ICR) mass spectrometry, and magnetic sector mass spectrometry.

23. (previously presented) A method of comparing protein profile maps, comprising:

a) providing:

i) a cell lysate derived from a cell of unknown type, said cell lysate comprising a plurality of proteins;

ii) a first protein profile map generated by the method of Claim 1;

iii) a separating apparatus, wherein said separating apparatus separates proteins based on a physical property; and

iv) a mass spectroscopy apparatus; and

b) treating said cell lysate with said separating apparatus to produce a separated protein sample; wherein said separated protein sample is collected from said separating apparatus in a plurality of fractions, each of said fractions defined by a physical property;

c) analyzing said plurality of fractions from said separated protein sample with said mass spectroscopy apparatus to produce a second protein profile map, wherein said second protein profile maps displays each protein as a separate band corresponding to said mass of said first protein sample and said second protein sample, and wherein the intensity of said band corresponds to said protein abundance of said first protein sample and said second protein sample; and

d) comparing said first protein profile map and said second protein profile map, wherein said first and second protein profile maps are displayed side by side.

24. (original) The method of Claim 23, wherein said first protein profile map displays protein abundance and mass from cell lysates of several known cell types and said second protein profile map displays protein abundance and mass from said cell lysate of unknown type.

25. (canceled)

26. (previously presented) The method of Claim 23, wherein said bands are bands of different colors.

27. (original) The method of Claim 24, wherein said protein abundance and mass are indicative of a cell identity.

28. (previously presented) A system for the production of a data representation of a protein profile map, comprising:

a) a non-porous reverse phase HPLC separating apparatus;

b) an automated sample handling apparatus configured to receive first and second separated protein samples from said reverse phase HPLC separating apparatus;

c) a mass spectroscopy apparatus configured to receive proteins from said automated sample handling apparatus;

d) a processor configured to produce a data representation of a protein profile map for said first and second separated protein samples analyzed by said mass spectroscopy apparatus, wherein said protein profile map displays protein abundance and mass of a separated protein sample, wherein said protein profile map displays proteins as separate bands corresponding to said protein abundance and mass of said separated protein sample, and wherein the intensity of said bands corresponds to the abundance of said proteins, wherein said protein profile maps for each of said first and second samples are displayed side by side; and

e) a display apparatus that displays said protein profile maps.

29. (original) The system of Claim 28, wherein said protein profile map displays protein abundance as bands of varying intensity.

30. (original) The system of Claim 29, wherein said protein abundance is expressed as bands of different colors.

31. (original) The system of Claim 28, wherein said protein abundance and mass are indicative of a cell type of said protein sample.

32. (original) The system of Claim 28, wherein said processor is configured to determine the identity of individual bands on said protein profile map.

33. (original) The system of Claim 28, wherein said automated sample handling device comprises a switchable, multi-channel valve.

34. (previously presented) The system of Claim 28, wherein said mass spectrometry apparatus comprises a electrospray ionization-orthogonal acceleration-time-of-flight mass spectrometry apparatus.

35. (previously presented) A method of producing protein profile maps, comprising:

a) providing:

i) a first sample comprising a plurality of proteins;

ii) a second sample comprising a plurality of proteins;

iii) a separating apparatus, wherein said separating apparatus separates proteins based on a physical property;

iv) a mass spectroscopy apparatus; and

b) treating said first and second samples with said separating apparatus to produce a first separated protein sample and a second separated protein sample, wherein

said first and second separated protein samples are collected from said separating apparatus in a plurality of fractions, each of said fractions defined by a physical property;

c) analyzing said plurality of fractions from each of said first and second separated protein samples with said mass spectroscopy apparatus to produce first and second protein profile maps for each of said first and second protein samples, wherein said protein profile maps display protein abundance and mass of said first protein sample and said second protein sample; and

d) displaying a differential display protein map of said first and second protein profile maps, wherein said differential display protein map displays the difference in protein abundance versus mass between proteins in said first and second protein samples, and wherein said differential display protein profile map displays the difference in protein abundance between each protein as a separate band corresponding to said mass of said first protein sample and said second protein sample, and wherein the intensity of said band corresponds to the difference in protein abundance.

36. (previously presented) The method of claim 35, further comprising the step of displaying said first and second protein profile maps.

37. (previously presented) The method of claim 36, wherein said first and second protein profile maps and said differential display map are displayed side by side.